Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.

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Bacterial Enteric Infections (Last updated August 10, 2017; last reviewed June 26, 2019)

NOTE: Update in Progress

Epidemiology

Rates of Gram-negative bacterial enteric infections are at least 10-fold higher among HIV-infected adults than in the general population, but these rates decline when patients are treated with antiretroviral therapy (ART).[1-7] The risk of bacterial diarrhea varies according to CD4 T lymphocyte (CD4) count and is greatest in individuals with clinical AIDS or <200 CD4 cells/mm^3.[5] The bacteria most frequently isolated by culture from HIV-infected adults in the United States are *Salmonella* (particularly *Salmonella enterica* serotypes Typhimurium and Enteritidis), *Shigella*, and *Campylobacter*. Diarrheagenic *Escherichia coli*, particularly enteroaggregative *E. coli*, may contribute to the burden of diarrheal disease,[8] but their role is poorly understood because diagnosis remains a research-only test. *Clostridium difficile*-associated infection (CDI) is common in HIV-infected patients; recent data[9] suggest that low CD4 count (<50 cells/mm^3) is an independent disease risk factor in addition to the traditional risk factors such as exposure to a health care facility or to antibiotics. Incidence of community-onset CDI is increasing and health care providers should also consider CDI in the evaluation of outpatient diarrheal illnesses in HIV-infected individuals. Data on *Helicobacter pylori* infection in HIV infection are limited and do not suggest excess risk in HIV-infected individuals. Other enteric infections that may cause diarrhea, such as *Mycobacterium avium* complex (MAC) and cytomegalovirus, are discussed elsewhere in these guidelines.

As with bacterial enteric infections in HIV-uninfected persons, the probable source for most enteric infections in HIV-infected patients is ingestion of contaminated food or water.[3] Sexual activity with the potential for direct or indirect fecal-oral exposure also increases risk of infections, especially with *Shigella*[10] and *Campylobacter*[11] (see Appendix for further details). HIV-associated alterations in mucosal immunity or intestinal integrity and treatment with acid-suppressive agents may increase risk of enteric bacterial infections.

Clinical Manifestations

The three major clinical syndromes of infection with Gram-negative enteric bacteria among HIV-infected patients are:

- Self-limited gastroenteritis;
- More severe and prolonged diarrheal disease, potentially associated with fever, bloody diarrhea, and weight loss; and
- Bacteremia associated with extra-intestinal involvement, with or without concurrent or preceding gastrointestinal (GI) illness.[12-15]

Severe community-associated diarrhea is often defined as ≥6 loose stools (loose stool is defined as defecated material that takes the shape of a container) per day with or without other signs of disease such as fecal blood, orthostatic hypotension, or fever. In HIV-infected patients, the risk of more profound illness increases with the degree of immunosuppression.[1,3,4,16] Relapses in infection with *Salmonella* and other Gram-negative bacterial enteric pathogens after appropriate treatment have been well documented in HIV-infected patients.[17-19]

Diagnosis

Assessment of patients with diarrhea should include a complete exposure history (see below); a medication review, because diarrhea is a common side effect of some ART and antibiotics; quantification of the diarrheal illness by stool frequency, volume, duration, and presence of blood; and associated signs and symptoms, such as presence and duration of fever. Physical examination should include measurement of temperature and

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assessment of volume and nutritional status.

The diagnosis of Gram-negative bacterial enteric infection is established through cultures of stool and blood. Stool cultures are required to obtain antibiotic sensitivity testing for isolated enteric pathogens. Thus, stool cultures are preferred over or in addition to molecular diagnostics in HIV-infected patients given increasing resistance detected in enteric bacterial infections. Because incidence of bacteremia associated with *Salmonella* gastroenteritis is high in HIV-infected individuals, particularly those with advanced disease, blood cultures should be obtained from any patient with diarrhea and fever. For shigellosis, blood cultures may be helpful but are less likely to be positive than in salmonellosis.

Other infections for which HIV-infected patients are at risk, albeit at a lower rate, are non-*jejuni* non-coli *Campylobacter* species, such as *Campylobacter fetus*, *Campylobacter upsaliensis*, and *Campylobacter lari*, and the enterohepatic *Helicobacter* spp. (*Helicobacter cineadi* and *Helicobacter fennelliae*), which were originally described as *Campylobacter* spp. Blood culture systems will typically grow these bacteria, but they are unlikely to be identified on routine stool cultures performed by most laboratories because growing these fastidious organisms requires special stool culture conditions.

A stool sample for *C. difficile* toxin or polymerase chain reaction (PCR) assay should be routinely performed for patients with diarrhea who have recently received or are currently receiving antibiotics (including antimicrobial prophylaxis) or cancer chemotherapy, those who have been hospitalized in the past 4 to 6 weeks (or are currently hospitalized), those who reside in a long-term care facility, those with CD4 counts <200 cells/mm^3, those taking acid-suppressive medications, and those with moderate-to-severe community-acquired diarrhea.[20] The most commonly used toxin tests are enzyme immunoassays that suffer from low sensitivity. PCR assays or glutamate dehydrogenase antigen enzyme immunoassays (which must be combined with a second confirmatory test for stool toxin) are recommended for testing.[21] However, only diarrheal stool samples should be tested for *C. difficile* to limit detection of asymptomatic colonization. Regardless of the test used, the diagnosis of CDI can only be made through careful selection of the correct population for testing and a correlation of clinical and laboratory findings.

Endoscopy should generally be reserved for patients in whom stool culture, microscopy, *C. difficile* toxin assay, and blood culture fail to reveal an etiology or in whom treatment for an established diagnosis fails. Endoscopy with biopsy may be required for diagnosing etiologies other than bacterial enteric infections, including cryptosporidiosis, microsporidiosis, cytomegalovirus or MAC gastroenteritis, and noninfectious causes of GI symptoms.

Clinicians should remain alert to the possibility of sexually transmitted disease (STD). Some sexually transmitted rectal infections (e.g., proctitis due to lymphogranuloma venereum or *Neisseria gonorrhoeae*) can produce symptoms similar to those seen with colitis due to *Salmonella*, *Shigella*, and *Campylobacter* spp. If stool cultures fail to yield enteric bacterial pathogens in patients with symptoms of proctitis or colitis, diagnostic evaluation for STDs with anoscopy, culture, and biopsy should be considered.

Preventing Exposure

Multiple epidemiologic exposures can place patients at risk of enteric illnesses. The most common are ingestion of contaminated food or water and fecal-oral exposures (detailed prevention recommendations related to food and water exposures, pet exposures, and travel-related exposures can be found in the Appendix). Providing advice and education about such exposures is the responsibility of the health care provider. A patient's clinical condition and CD4 count can help the provider determine what prevention recommendations are most appropriate. Patients with CD4 counts <200 cells/mm^3 or a history of AIDS-defining illness[22] are at the greatest risk of enteric illnesses;[5] however, excess risk of undetermined magnitude or duration may persist in those with lesser degrees of immune impairment, including individuals treated with ART.

Patients should be advised to regularly wash their hands with soap and water or alcohol-based cleansers to reduce the risk of enteric infection **(AIII)**. With regard to preventing enteric infection, soap and water are

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preferred over alcohol-based cleansers, which do not kill *C. difficile* spores and are only partially active against norovirus and *Cryptosporidium* **(AIII)**. HIV-infected patients should be advised to wash their hands after potential contact with human feces (e.g., as through defecation, cleaning feces from infants, or contact with a person who has diarrhea), after handling pets or other animals, after gardening or other contact with soil, before preparing food and eating, and before and after sex **(AIII)**. HIV-infected patients should avoid unprotected sex practices, such as anal sex and oral-anal contact that could result in oral exposure to feces and, in addition to handwashing, they should be advised to use barriers such as dental dams during sex to reduce exposures when possible **(AIII)**.

Preventing Disease

Antimicrobial prophylaxis to prevent bacterial enteric illness **is usually not recommended**, including for travelers **(AIII)**. Prophylactic antimicrobial treatment can elicit adverse reactions, promote the emergence of resistant organisms, and increase risk of CDI. In rare cases, however, antimicrobial prophylaxis with fluoroquinolones or rifaximin can be considered, such as for immunosuppressed travelers, depending on their level of immunosuppression, the region of travel, and the trip's duration **(CIII)**. For pregnant women and patients already taking trimethoprim-sulfamethoxazole (TMP-SMX) (such as for *Pneumocystis jirovecii* pneumonia prophylaxis), TMP-SMX may offer limited protection against travelers' diarrhea as an alternative to fluoroquinolones or rifaximin **(BIII)**. Risk of toxicity should be considered before prophylaxis with TMP-SMX is initiated solely because of travel.

Treating Disease

Empiric Therapy

In most situations, treatment of diarrheal disease in HIV-infected patients does not differ significantly from that in immunocompetent individuals. Decisions on therapy are based on an assessment of diarrhea severity and hydration status. Patients should be informed of the importance of maintaining hydration and be given oral or intravenous (IV) rehydration, if indicated **(AIII)**. Because diarrheal disease can produce temporary malabsorption or lactose intolerance, consuming a bland diet and avoiding fat, dairy, and complex carbohydrates also are likely to be useful **(BIII)**. The effectiveness and safety of probiotics or antimotility agents have not been adequately studied in HIV-infected patients with diarrheal illnesses.[23] Antimotility agents should be avoided if there is concern about inflammatory diarrhea, including CDI **(BIII)**.

After obtaining stool samples for diagnostic evaluation, initiation and duration of empiric antimicrobial therapy depend upon the patient's CD4 count and clinical appearance. If stool samples are obtained, antibiotic susceptibility testing should be performed to confirm and inform antibiotic choice. No further work-up may be necessary and no treatment other than oral rehydration may be required, for example, in patients with CD4 counts >500 cells/mm^3 who have had 1 to 2 days of loose stools without fever or blood. However, a short course of antibiotics may be indicated in HIV-infected patients with CD4 counts of 200 to 500 cells/mm^3 who have diarrhea severe enough to compromise quality of life or ability to work. Patients with advanced HIV disease (i.e., CD4 counts <200 cells/mm^3 or concomitant AIDS-defining illness) and clinically severe diarrhea (i.e., ≥6 liquid stools per day or bloody stools or a lower number of liquid stools per day but accompanied by fever or chills concerning for invasive bacterial disease) should undergo diagnostic evaluation to determine the etiology of the diarrheal illness and receive antimicrobial treatment. Empiric therapy with ciprofloxacin is reasonable **(AIII)**. IV ceftriaxone or IV cefotaxime are reasonable alternatives **(BIII)**. Therapy should be adjusted subsequently based on the results of the diagnostic work-up. Diarrhea that is persistent (i.e., lasting >14 days) in the absence of other clinical signs of severity, such as bloody stool or dehydration, should be evaluated and directed therapy should be started once a diagnosis is confirmed.

Diarrhea is one of the most common illnesses affecting international travelers. Antimicrobial resistance among enteric bacterial pathogens outside the United States is an important public health problem. For example, traveler's diarrhea caused by fluoroquinolone-resistant *Campylobacter jejuni* in Southeast Asia is common.[24] Clinicians should consider the possibility of a resistant infection when prescribing empiric

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therapy for HIV-infected travelers who experience diarrhea or a syndrome consistent with a systemic infection while traveling or upon returning to the United States, given reports of multidrug resistant *Enterobacteriaceae* acquisition during travel.[25-29]

Pathogen-Specific Therapy

Salmonella spp.

Immunocompetent hosts who are not HIV-infected often do not require treatment for *Salmonella* gastroenteritis, as the condition is usually self-limited and treatment may prolong the carrier state. In contrast, all HIV-infected patients with salmonellosis should be treated **(AIII)**, although no clinical trials have compared antimicrobial therapy with placebo. Notably, HIV infection increases the risk of *Salmonella* bacteremia 20- to 100-fold and mortality as much as 7-fold compared with that in patients who are not HIV-infected.[1,30]

The initial treatment of choice for *Salmonella* infection is a fluoroquinolone **(AIII)**. Ciprofloxacin is the preferred agent **(AIII)**.[31] Other fluoroquinolones, such as levofloxacin and moxifloxacin, would likely be effective in treating salmonellosis in HIV-infected patients but they have not been well evaluated in clinical studies **(BIII)**. Depending on antibiotic susceptibility, alternatives to the fluoroquinolones might include TMP-SMX or expanded-spectrum cephalosporins such as ceftriaxone or cefotaxime **(BIII)**.

The optimal duration of therapy for HIV-related *Salmonella* infection has not been defined. For patients with CD4 counts ≥200 cells/mm^3 who have mild gastroenteritis without bacteremia, 7 to 14 days of treatment is reasonable. For the same patients with bacteremia, 14 days is appropriate, provided clearance of bacteremia is documented. Longer treatment is suggested if bacteremia persists or if the infection is complicated, that is, if metastatic foci are present **(BIII)**. For patients with advanced HIV disease (CD4 count <200 cells/mm^3), 2 to 6 weeks of antibiotics is often recommended **(CIII)**.[32] Some patients with *Salmonella* bacteremia may remain febrile for 5 to 7 days despite effective therapy.

HIV-infected patients with *Salmonella* bacteremia, which typically occurs in those with advanced HIV disease, should be monitored clinically for recurrence after treatment **(BIII)**. Recurrence may present as bacteremia or as an anatomically localized infection, including intra-abdominal, endothelial, urinary tract, soft tissue, bone and joint, lung, or meningeal foci. Secondary prophylaxis should be considered for patients with recurrent *Salmonella* bacteremia **(BIII)** and it might also be considered for patients with recurrent gastroenteritis (with or without bacteremia) and in those with CD4 counts <200 cell/mm^3 with severe diarrhea **(BIII)**. The value of this secondary prophylaxis has not been established and must be weighed against the risks of long-term antibiotic exposure. Recurrent *Salmonella* bacteremia constitutes an AIDS-defining illness[33] and suppression of HIV replication with ART appears to decrease the risk of recurrent illnesses.[34] In patients whose *Salmonella* infection is resolved and who have responded to ART with sustained viral suppression and CD4 counts >200 cells/mm^3, secondary prophylaxis for salmonellosis can probably be stopped **(CII)**.[7] Clinicians also should be aware that recurrence may represent development of antimicrobial resistance during therapy.

Shigella spp.

Therapy for *Shigella* infections is recommended both to shorten the duration of illness and to possibly prevent spread of the infection to others **(AIII)**.[31] The recommended treatment for shigellosis is with a fluoroquinolone, preferably ciprofloxacin, for 7 to 10 days **(AIII)**. Although current CLSI criteria categorizes *Shigella* isolates with MIC 0.12-1 ug/ml as susceptible, these isolates may harbor plasmid-mediated resistance genes. Until the clinical significance of these findings can be determined, fluoroquinolones should only be used to treat isolates with MIC <0.12 ug/ml.[35] Ciprofloxacin-resistant *S. sonnei* and *S. flexneri* have been reported in the United States and are associated with international travel, homelessness, and being a man who has sex with men (MSM); ciprofloxacin-resistant shigellosis among MSM appears to be acquired predominantly within the United States, rather than during travel.[29] Depending on antibiotic susceptibilities, alternative agents might include TMP-SMX (7–10 days) or azithromycin (5 days) **(BIII)**. Azithromycin has

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not been evaluated in HIV-infected patients with shigellosis, and the therapy suggested is extrapolated from limited data in immunocompetent hosts.[36] Recently, azithromycin-resistant *Shigella* spp in HIV-infected MSM have been reported.[37-39] Treatment for patients with *Shigella* bacteremia is less well defined, but extending treatment to at least 14 days is reasonable **(BIII)**. Azithromycin **is not recommended** for treatment of *Shigella* spp. bacteremia **(AIII)**. Chronic suppressive or maintenance therapy **is not recommended** for first-time *Shigella* infections **(BIII)**. Recurrent infections can occur, particularly in individuals with CD4 counts <200 cells/mm^3, in which case extending antimicrobial therapy for up to 6 weeks is reasonable **(BIII)**. As with *Salmonella* infections, suppression of HIV replication with ART is expected to decrease the risk of recurrent shigellosis.

Campylobacter spp.

The optimal treatment of Campylobacteriosis in HIV-infected patients is poorly defined. Culture and testing for the antibiotic susceptibility of *Campylobacter* isolates is recommended **(BIII)**. Rates of resistance to antimicrobial agents differs by *Campylobacter* species. In the United States in 2013, 22% of *C. jejuni* isolates were resistant to fluoroquinolone and 2% were resistant to azithromycin; among *C. coli* isolates, 35% of isolates were resistant to fluoroquinolones and 17% were resistant to azithromycin.[40] For patients with mild disease and CD4 counts >200 cells/mm^3, some clinicians opt to withhold therapy unless symptoms persist for more than several days **(CIII)**. For mild-to-moderate Campylobacteriosis, initiating therapy with a fluoroquinolone such as ciprofloxacin for 7 to 10 days (if the organism is sensitive) or azithromycin for 5 days is a reasonable approach **(BIII)**. Azithromycin has not been evaluated in HIV-infected patients with Campylobacteriosis and the therapy suggested is extrapolated from limited data in immunocompetent hosts.[41] Patients with *Campylobacter* bacteremia should be treated for at least 14 days using a fluoroquinolone if the isolate is sensitive **(BIII)**. Azithromycin **is not recommended** for treatment of *Campylobacter* bacteremia **(AIII)**. Adding a second active agent, such as an aminoglycoside, may be prudent in these patients to limit the emergence of antibiotic resistance **(BIII)**. Antibiotic choice should be guided by antibiotic susceptibility tests. Chronic suppressive or maintenance therapy **is not recommended** for first-time *Campylobacter* infections in HIV-infected patients **(BIII)**. However, recurrent infections can occur, particularly in patients with CD4 counts <200 cells/mm^3. In recurrent disease, extending the length of antimicrobial therapy for 2 to 6 weeks is reasonable **(BIII)**. As with *Salmonella* infections, suppression of HIV replication with ART is expected to decrease the risk of recurrent *Campylobacter* spp. infections.

Clostridium difficile

Available data suggest that HIV-infected patients respond to treatment of CDI similarly to HIV-uninfected patients. Guidelines and subsequent updates to guide the treatment of CDI have been published[42-45] and can be consulted for further information. Multivariate analysis of 2 recent identical, multicenter (91 sites in United States, Canada; 109 sites in Europe), randomized, double-blind studies involving 537 non-HIV-infected patients with CDI (278 and 259 treated with metronidazole and vancomycin, respectively) found vancomycin to be superior to metronidazole for clinical success [OR 1.575 (1.035, 2.396), $P = 0.034$]. Stratification by CDI disease severity found 4.0% (mild), 8.3% (moderate), and 12.2% (severe) improved clinical success rates with vancomycin therapy compared to metronidazole therapy.[46] Given this trial and earlier data,[47] vancomycin **(AI)** is recommended for treatment of HIV-infected persons with CDI with the possible exception of mild CDI where treatment with metronidazole **(CII)** may yield clinical success. Treatment of recurrent CDI in HIV-infected patients is the same as in patients who are not HIV-infected. Limited case reports suggest that fecal microbiota therapy (aka fecal transplant) may be successful and safe to treat recurrent CDI in HIV-infected patients **(CIII)**.[48] The impact of ART on recurrence of CDI is unknown.

Special Considerations with Regard to Starting ART

ART initiation should follow standard guidelines. The presence of a diarrheal illness is relevant only in terms of a patient's ability to ingest and absorb ART. If recurrent enteric infections are documented or *Salmonella* bacteremia occurs, prompt initiation of ART should be considered regardless of CD4 count; in other words, the presence of an enteric infection should not delay ART initiation **(BIII)**.

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Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients should be monitored closely for response to treatment, defined clinically by improvement in systemic signs and symptoms, resolution of diarrhea, and sterilization of infected tissues or body fluids such as blood. A follow-up stool culture to demonstrate clearance of the organism is not required if clinical symptoms and diarrhea resolve. Follow-up stool culture may be required when public health considerations and state law dictate the need to ensure micro¬biologic cure, such as in health care or food service workers.

Immune reconstitution inflammatory syndrome has not been described in association with treatment for bacterial enteric pathogens.

Managing Treatment Failure

Follow-up stool culture should be considered for patients who fail to respond clinically to appropriate antimicrobial therapy. In patients with persistent or recurrent diarrhea despite therapy, clinicians should consider other enteric infections in the context of the patient's immune status and, in all cases, the possibility of *C. difficile* or the development of antimicrobial resistance.

Observational studies suggest that plasma drug concentrations (e.g., of ciprofloxacin) in HIV-infected patients may be decreased as a result of diarrhea or malabsorption.[49,50] Coadministration of quinolones with magnesium- or aluminum-containing antacids or with calcium, zinc, or iron should be avoided because these interfere with drug absorption. Although larger prospective studies are needed to determine the impact of severe diarrhea on antibiotic absorption, it is prudent to use IV antibiotics in clinically unstable patients **(AIII)**.

Preventing Recurrence

The pharmacologic approach to recurrent enteric infections is covered in the section on directed therapy for each bacterial species. As noted above, secondary prophylaxis should be considered for patients with recurrent *Salmonella* bacteremia **(BIII)** and, in some circumstances, for those with recurrent shigellosis **(BIII)** or Campylobacteriosis **(BIII)**.

Special Considerations During Pregnancy

The diagnosis of bacterial enteric infection in pregnant women is the same as in women who are not pregnant. Bacterial enteric infections in pregnant women should be managed the same as in women who are not pregnant, with several considerations. Based on the safety profile, expanded-spectrum cephalosporins or azithromycin should be the first-line therapy for bacterial enteric infections during pregnancy if antimicrobials are required, depending on the organism and the results of susceptibility testing **(BIII)**.[51] Arthropathy has been noted in the offspring of animals treated with quinolones during pregnancy. However, studies evaluating quinolone use in pregnant women did not find an increased risk of birth defects or musculoskeletal abnormalities.[52-54] Thus, quinolones can be used in pregnancy for bacterial enteric infections in HIV-infected pregnant women if indicated by susceptibility testing or failure of first-line therapy, as listed above **(BIII)**. TMP-SMX use in the first trimester should be avoided, if possible, because of an association with an increased risk of birth defects, specifically neural tube, cardiovascular, and urinary tract defects **(BIII)**.[55,56,57] However, a recent review of potential risks related to TMP-SMX use cites the low quality of current data and supports use of TMP-SMX in HIV-infected pregnant women as clinically indicated.[58] Neonatal care providers should be informed if maternal sulfa therapy was used near delivery because of the theoretical increased risk of hyperbilirubinemia and kernicterus in the newborn. Since rifaximin is not systemically absorbed, it can be used in pregnancy as in non-pregnant individuals. Limited data are available on the risks of vancomycin use during pregnancy, however minimal absorption is expected with oral therapy. With intravenous use, vancomycin readily crosses the placenta.[59] A study of 10 infants evaluated after second or third trimester in utero exposure from maternal intravenous vancomycin therapy for serious staphylococcal infections found no hearing loss or renal toxicity attributed to vancomycin.[60] A recent review of metronidazole use in pregnancy for treatment of trichomoniasis or bacterial vaginosis found no increase in risk of birth defects.[61] Studies on use for CDI in pregnancy were not found.

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Recommendations for Preventing and Treating Bacterial Enteric Infections (page 1 of 3)

Preventing Bacterial Enteric Illness

- Antimicrobial prophylaxis to prevent bacterial enteric illness usually **is not recommended**, including for travelers **(AIII)**.
- In rare cases, such as for immunosuppressed travelers, depending on their level of immunosuppression, the region of travel, and the trip's duration, antimicrobial prophylaxis with fluoroquinolones or rifaximin can be considered **(CIII)**.
- For pregnant women and patients already on trimethoprim-sulfamethoxazole (TMP-SMX) for prophylaxis against *Pneumocystis* pneumonia TMP-SMX may offer limited protection against travelers' diarrhea as an alternative to fluoroquinolone or rifaximin **(BIII)**.

General Considerations when Managing Patients with Bacterial Enteric Infections

- Oral or IV rehydration therapy (if indicated) should be given to patients with diarrhea **(AIII)**.
- Antimotility agents should be avoided if there is concern about inflammatory diarrhea, including *Clostridium difficile* infection (CDI) **(BIII)**.
- Diagnostic fecal specimens should be obtained prior to initiation of empiric antimicrobial therapy.
- If stool sample is obtained, antibiotic susceptibilities should be performed to confirm and inform antibiotic choice given increased reports of antibiotic resistance.
- Risk of a bacterial enteric infection increases as CD4 count declines, with the greatest risk in patients with CD4 counts <200 cells/mm^3. Risk of bacteremia also increases with decreasing CD4 count. If no clinical response after 3 to 4 days, consider follow-up stool culture with antibiotic susceptibility testing and other methods to detect enteric pathogens (e.g., toxin assays, molecular methods), alternative diagnosis, antibiotic resistance, or drug-drug interactions.
- Effective ART may reduce the frequency, severity, and recurrence of bacterial enteric infections.

Empiric Treatment of Bacterial Enteric Infections (Pending Diagnostic Studies)

For patients with advanced HIV (CD4 count <200 cells/mm^3 or concomitant AIDS-defining illnesses) and clinically severe diarrhea (≥6 liquid stools/day or bloody stool and/or accompanying fever or chills).

Preferred Therapy:

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(AIII)**

Alternative Therapy:

- Ceftriaxone IV 1 g q24h **(BIII)**, *or*
- Cefotaxime IV 1g q8h **(BIII)**

Note: IV antibiotic therapy with hospitalization should be considered in patients with marked nausea, vomiting, diarrhea, electrolyte abnormalities, acidosis, blood pressure instability, and/or when clinical judgment indicates severity of disease.

For patients with persistent diarrhea (>14 days) but no other severe clinical signs (e.g., dehydration, blood in stool), antibiotic therapy can be withheld until a diagnosis is confirmed.

Diarrhea is a common illness of international travelers. Antimicrobial resistance among enteric bacterial pathogens outside the United States is common. Clinicians should consider the possibility of resistant infections when prescribing empiric antibiotic therapy for HIV-infected travelers while traveling or upon return to the United States, particularly among travelers to South and Southeast Asia.

Treating Salmonellosis

All HIV-infected patients with salmonellosis should receive antibiotic treatment due to the increased risk of bacteremia (by 20–100-fold) and mortality (by as much as 7-fold) compared with HIV-negative individuals **(AIII)**.

Preferred Therapy for Salmonella Gastroenteritis With or Without Bacteremia:

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(AIII)**

Alternative Therapy:

- Levofloxacin 750 mg (PO or IV) q24h **(BIII)**, *or*
- Moxifloxacin 400 mg (PO or IV) q24h **(BIII)**

If susceptible, alternatives to fluoroquinolone may include 1 of the following:

- Trimethoprim 160 mg/sulfamethoxazole 800 mg (PO or IV) q12h **(BIII)**, *or*
- Ceftriaxone IV 1g q24h **(BIII)**, *or*
- Cefotaxime IV 1g q8h **(BIII)**

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Treating Salmonellosis, *continued*

Duration of Therapy for Gastroenteritis Without Bacteremia

- If CD4 count >200 cells/mm^3: 7–14 days **(BIII)**
- If CD4 count <200 cells/mm^3 particularly if primary illness was severe: 2–6 weeks **(BIII)**

Duration of Therapy for Gastroenteritis With Bacteremia

- If CD4 count >200 cells/mm^3: 14 days; longer duration if bacteremia persists or if the infection is complicated (e.g., metastatic foci of infection are present) **(BIII)**
- If CD4 count <200 cells/mm^3: 2–6 weeks **(BIII)**

Secondary Prophylaxis

The role of long-term, secondary prophylaxis for patients with recurrent bacteremia or gastroenteritis is not well established. Clinicians must weigh the benefit against the risks of long-term antibiotic exposure **(BIII)**. Antibiotic choices for secondary prophylaxis are the same as for primary treatment and are dependent on the sensitivity of the *Salmonella* isolate.

Suppression of HIV replication with ART is expected to decrease the risk of recurrent illnesses.

Clinicians should be aware that recurrence may represent development of antimicrobial resistance during therapy.

Some Experts Recommend Secondary Prophylaxis for:

- Patients with recurrent bacteremia, *or*
- Patients with recurrent gastroenteritis (with or without bacteremia) with CD4 count <200 cells/mm^3 and severe diarrhea **(CIII)**

When to Stop Secondary Prophylaxis:

- After resolution of *Salmonella* infection and response to ART with sustained viral suppression and CD4 count >200 cells/mm^3 **(CII)**

Treating Shigellosis

Therapy is indicated to shorten the duration of illness and to possibly prevent spread to others **(AIII)**. However, given increasing antimicrobial resistance and limited data demonstrating that antibiotic therapy limits transmission, antibiotic treatment may be withheld in HIV-infected patients with CD4 >500 cells/mm^3 whose diarrhea resolves prior to culture confirmation of *Shigella* infection **(CIII)**.

Preferred Therapy:

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h if MIC<0.12 ug/ml (see **Note**) **(AIII)**

Alternative Therapy (Depending on Susceptibility Results):

- Levofloxacin 750 mg (PO or IV) q24h **(BIII)**, *or*
- Moxifloxacin (PO or IV) 400 mg q24h **(BIII)** *or*
- Trimethoprim 160 mg/sulfamethoxazole 800 mg PO or IV q12h **(BIII)** *or*
- Azithromycin 500 mg PO daily for 5 days **(BIII)** (Note: Azithromycin **is not recommended** for *Shigella* bacteremia **[AIII]**)

Duration of Therapy:

- Gastroenteritis: 7–10 days **(AIII)** (except azithromycin, treat for 5 days)
- Bacteremia: ≥14 days **(BIII)**
- Recurrent infections: up to 6 weeks **(BIII)**

Chronic Maintenance or Suppressive Therapy:

- Not recommended for first-time *Shigella* infections **(BIII)**

Note: Increased resistance of *Shigella* to fluoroquinolones is occurring in the United States. Avoid treating *Shigella* with fluoroquinolones if ciprofloxacin MIC is ≥0.12 ug/ml even if the laboratory identifies the isolate as sensitive. Many *Shigella* strains resistant to fluoroquinolones exhibit resistance to other commonly used antibiotics. Thus, antibiotic sensitivity testing of *Shigella* isolates from HIV-infected individuals should be performed routinely.

Treating Campylobacteriosis

- Optimal treatment is poorly defined.
- There is an increasing rate of fluoroquinolone resistance in the United States (22% resistance in 2013 among *C. jejuni* isolates).
- Antimicrobial therapy should be modified based on susceptibility reports.

Mild Disease if CD4 Count >500 cells/mm^3:

- If diarrhea resolves prior to culture confirmation of *Campylobacter* infection, antibiotic treatment can be withheld **(CIII)**. If symptoms persist, consider antibiotic therapy **(CIII)**.

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Treating Campylobacteriosis, *continued*

Mild to Moderate Disease

Preferred Therapy:

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(BIII)**—if susceptible, *or*
- Azithromycin 500 mg PO daily for 5 days **(BIII)** (**Not recommended** for bacteremia **[AIII]**)

Alternative Therapy (Depending on Susceptibility Results):

- Levofloxacin 750 mg PO or IV q24h **(BIII)**, *or*
- Moxifloxacin 400 mg PO or IV q24h **(BIII)**

Bacteremia:

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(BIII)** plus an aminoglycoside **(BIII)** in bacteremic patients to limit the emergence of antibiotic resistance

Duration of Therapy:

- Gastroenteritis: 7–10 days **(BIII)** [5 days if azithromycin is used]
- Bacteremia: ≥14 days **(BIII)**
- Recurrent bacteremic disease: 2–6 weeks **(BIII)**

Chronic Maintenance or Suppressive Therapy:

- Not recommended for first-time *Campylobacter* infections **(BIII)**

Treating *Clostridium difficile* Infection (CDI)

Preferred Therapy:

- Vancomycin 125 mg (PO) 4 times per day for 10–14 days **(AI)**
- For severe, life-threatening CDI, see text and references for additional information.

Alternative Therapy for Mild CDI:

- For mild, outpatient disease: metronidazole 500 mg (PO) 3 times per day for 10-14 days **(CII)**

Recurrent CDI:

- Treatment is the same as in patients without HIV infection. Fecal microbiota therapy (FMT) may be successful and safe to treat recurrent CDI in HIV-infected patients **(CIII)**. See text and references for additional information.

Key to Acronyms: CD4 = CD4 T lymphocyte cell; IV = intravenously; PO = orally; q(n)h = every "n" hours.

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